jc713 U.S. PTO
01/10/00

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jc662 U.S. PTO
09/479862
01/10/00

January 10, 2000

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

RE: New Divisional Patent Application in U.S.
Applicant(s): Takanori OKURA et al.
Title: GENOMIC DNA ENCODING A POLYPEPTIDE CAPABLE OF INDUCING THE PRODUCTION OF INTERFERON-γ
Atty's Docket: OKURA=1A

Sir:

Attached herewith is the above-identified application for Letters Patent including:

[X] Specification (29 pages), claims (4 pages) and abstract (1 page)
[X] 1 Sheet Drawings (Figure 1)
  [X] Formal [ ] Informal
[X] Declaration and Power of Attorney (pages)
  [ ] Newly executed [X] Copy from prior application no. 08/884,324
[X] Preliminary Amendment
  [ ] Computer-readable Sequence Listing
[ ] Supplemental Preliminary Amendment
[ ] Information Disclosure Statement with ( ) references
[ ] A verified statement to establish small entity status under 37 CFR §1.9 and 37 CFR §1.27 (page(s))
[X] A check in the amount of $ 760.00 (check no. 24556) to cover:
[X] The filing fee calculated as follows (including any preliminary amendment for entry prior to calculation of the filing fee):

CLAIMS AS FILED				
FOR	NUMBER FILED	NUMBER EXTRA	RATE	BASIC FEE $ 760.00
TOTAL CLAIMS	17 - 20	= 0	x 18	--
INDEPENDENT CLAIMS	3 - 3	= 0	x 78	--
[ ] Multiple Dependent Claim Presented			x260	--
[ ] Reduction of ½ for small entity				-$
		TOTAL FILING FEE		$ 760.00

In re of

[ ] Any additional fee required by the filing of an enclosed preliminary or supplemental preliminary amendment (for entry after calculation of the filing fee) has been calculated as shown below:

	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	CALCULATION
TOTAL		-	=	X $18.00	$
INDEP		-	=	x 78.00	$
[ ] Multiple Dependent Claim Presented				x $260.00	$
Total of Above Calculations =					$
Reduction by ½ for filing by small entity					-$
Total Additional Fee =					$

[ ] Other Fees: ________________________________.

[ ] Other Attachments: ________________________________.

[X] Return Receipt Postcard (in duplicate)

The following statements are applicable:

[X] The benefit under 35 U.S.C. §119 is claimed of the filing date of: Application No. 185305/1996 in Japan on 27 June 1996. A certified copy of said priority document [ ] is attached [X] was filed in progenitor case 08/884,324 on October 6, 1997.

[X] The present application is a [ ] Continuation [X] Division [ ] Continuation-in-part of prior application No. 08/884,324.

[X] Incorporation By Reference. The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied herewith, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

[ ] A signed statement deleting inventor(s) named in the prior application is attached.

[X] The prior application was assigned to: KABUSHIKI KAISHA HAYASHIBARA SEIBUTSU SAGAKU KENKYUJO, 2-3, 1-chome, Shimoishii, Okayama-shi, Okayama, Japan.

[ ] Amend the specification by inserting before the first line the sentence: --This is a ___ continuation ___ division of copending parent application Serial No. , filed ________________.--

[X] Certain documents were previously cited or submitted to the Patent and Trademark Office in the following prior application 08/884,324, which is relied upon under 35 U.S.C. §120. Applicants identify these documents by attaching hereto a form PTO-1449 listing these documents, and request that they be considered and made of record in accordance with 37 CFR §1.98(d). Per Section 1.98(d), copies of these documents need not be filed in this application.

[ ] A verified statement claiming small entity status is enclosed in progenitor application no.____________ , filed _____________. Status is still proper and desired.

In re of

[X] The paper copy of the Sequence Listing in this application is identical to the computer-readable copy of the Sequence Listing filed June 27, 1997, in application no. 08/884,324. In accordance with 37 CFR §1.821(e), please use the last-filed computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the instant application. A paper copy of the Sequence Listing is included in the originally-filed specification of the instant application (or included in a separately filed preliminary amendment for incorporation into the specification).

[ ] The undersigned attorney of record hereby revokes the powers of attorney of:

[ ] The undersigned attorney of record hereby appoints associate power of attorney, to prosecute this application and to transact all business in the Patent and Trademark Office in connection therewith to:

[X] The Commissioner is hereby authorized to charge payment of the following additional fees associated with this communication or credit any overpayments to Deposit Account No. 02-4035:
- [X] Any additional filing fees required under 37 CFR §1.16.
- [X] Any patent application processing fees under 37 CFR §1.17.

[X] The Commissioner is hereby authorized to charge payment of the following fees, based on any paper filed during the pendency of this application or any CPA thereof, to effect any amendment, petition, or other action requested in said paper or credit any overpayments to Deposit Account No. 02-4035:
- [X] Any patent application processing fees under 37 CFR §1.17.
- [ ] The issue fee set in 37 CFR §1.18 at or before mailing the Notice of Allowance, pursuant to 37 CFR §1.311(b).
- [X] Any filing fees under 37 CFR §1.16 for presentation of extra claims.
- [X] If a paper is untimely filed in this or any CPA thereof by Applicant(s), the Commissioner is hereby petitioned under 37 CFR §1.136(a) for the minimum extension of time required to make said paper timely. In the event a petition for extension of time is made under the provisions of this paragraph, the Commissioner is hereby requested to charge any fee required under 37 CFR §1.17 to Deposit Account 02-4035.

[X] The Commissioner is hereby authorized to credit any overpayment of fees accompanying this paper to Deposit Account No. 02-4035.

Respectfully submitted,
BROWDY AND NEIMARK, P.L.L.C.

By: ____________________
Allen C. Yun
Registration No. 37,971

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: OKURA=1A

In re Application of:	)	Art Unit:
Takanori OKURA et al.	)	Examiner:
Serial No.: NOT YET ASSIGNED (Divisional of 08/884,324)	)	Washington, D.C.
Filed: ON EVEN DATE HEREWITH	)	January 10, 2000
For: GENOMIC DNA ENCODING A POLYPEPTIDE CAPABLE OF...	)	

PRELIMINARY AMENDMENT

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Contemporaneous with the filing of this case and prior to calculation of a filing fee and examination on the merits, kindly amend as follows:

IN THE SPECIFICATION

Page 1, after the title and before "Background of the Invention", insert -- CROSS-REFERENCE TO RELATED APPLICATIONS

This is a divisional of copending parent application serial no. 08/884,324, filed June 27, 1997.--

Page 12, line 24, after "ggc-3'", insert --(SEQ ID NO:16)--; and

line 26, after "tgc-3'", insert --(SEQ ID NO:17)--.

Page 13, line 13, after "ggt-3'", insert --(SEQ ID NO:18)--; and

Division of 08/884,324

line 15, after "tgc-3'", insert --(SEQ ID NO:19)--.

Page 14, line 16, after "tcc-3'", insert --(SEQ ID NO:20)--; and

line 25, after "cac-3'", insert --(SEQ ID NO:21)--.

Page 15, line 14, after "cgg-3'", insert --(SEQ ID NO:22)--; and

line 18, after "ttg-3'", insert --(SEQ ID NO:23)--.

Page 16, line 12, after "tgc-3'", insert --(SEQ ID NO:24)--; and

line 16, after "-3'", insert --(SEQ ID NO:25)--.

Page 17, line 4, after "atc-3'", insert --(SEQ ID NO:26)--;

line 8, after "ttg-3'", insert --(SEQ ID NO:27)--;

line 22, after "ctc-3'", insert --(SEQ ID NO:28)--; and

line 26, after "ttg-3'", insert --(SEQ ID NO:29)--.

Page 18, line 11, after "tcc-3'", insert --(SEQ ID NO:30)--; and

line 20, after "tac-3'", insert

--(SEQ ID NO:31)--.

Page 19, line 11, change eukalyotic" to read --eukaryotic--;

line 25, delete "Patent Kokai No. 193,098/96", and insert therefor --patent application--.

Page 20, line 15, after "gta-3'", insert --(SEQ ID NO:32)--; and

line 18, after "ttg-3'", insert --(SEQ ID NO:33)--.

Page 21, line 5, after "-3'", insert --(SEQ ID NO:34)--; and

line 8, after "atc-3'", insert --(SEQ ID NO:35)--.

Page 22, line 19, change "abut" to read --about--.

Page 26, line 20, delete "or without"; and

line 21, delete "or 50 units/ml recombinant human interleukin 2".

Page 27, lines 17-18 from the bottom, delete "The IFN-γ production is enhanced in combination with concanavalin A or interleukin 2 as a cofactor."

REMARKS

The amendments to the specification are made to provide consistency with the specification as amended in the parent application.

Division of 08/884,324

Favorable consideration is respectfully solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
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Genomic DNA encoding a polypeptide capable of inducing the production of interferon-γ

Background of the Invention

Field of the Invention

The present invention relates to a genomic DNA, more particularly, a genomic DNA encoding a polypeptide capable of inducing the production of interferon-γ (hereinafter abbreviated as "IFN-γ") by immunocompetent cells.

Description of the Prior Art

The present inventors successfully isolated a polypeptide capable of inducing the production of IFN-γ by immunocompetent cells and cloned a cDNA encoding the polypeptide, which is disclosed in Japanese Patent Kokai No.27,189/96 and 193,098/96. Because the present polypeptide possesses the properties of enhancing killer cells' cytotoxicity and inducing killer cells' formation as well as inducing IFN-γ, a useful biologically active protein, it is expected to be widely used as an agent for viral diseases, microbial diseases, tumors and/or immunopathies, etc.

It is said that a polypeptide generated by a gene expression may be partially cleaved and/or glycosylated by processing with intracellular enzymes in human cells. A polypeptide to be used in therapeutic agents should be preferably processed similarly as in human cells, whereas human cell lines generally have a disadvantage of less producing the present polypeptide, as described in Japanese Patent Application No.269,105/96. Therefore, recombinant DNA techniques should be

applied to obtain the present polypeptide in a desired amount. To produce the polypeptide processed similarly as in human cells using recombinant DNA techniques, mammalian cells should be used as the hosts.

Summary of the Invention

In view of foregoing, the first object of the present invention is to provide a DNA which efficiently expresses the polypeptide production when introduced into a mammalian host cell.

The second object of the present invention is to provide a transformant into which the DNA is introduced.

The third object of the present invention is to provide a process for preparing a polypeptide, using the transformant.

[Means to Attain the Object]

The present inventors' energetic studies to attain the above objects succeeded in the finding that a genomic DNA encoding the present polypeptide efficiently expresses the polypeptide production when introduced into mammalian host cells. They found that the polypeptide thus obtained possessed significantly higher biological activities than that obtained by expressing a cDNA encoding the polypeptide in *Escherichia coli*.

The first object of the present invention is attained by a genomic DNA encoding a polypeptide with the amino acid sequence of SEQ ID NO:1 (where the symbol "Xaa" means "isoleucine" or "threonine") or its homologous one, which

induces interferon-γ production by immunocompetent cells.

The second object of the present invention is attained by a transformant formed by introducing the genomic DNA into a mammalian host cell.

The third object of the present invention is attained by a process for preparing a polypeptide, which comprises (a) culturing the transformant in a nutrient medium, and (b) collecting the polypeptide from the resultant culture.

Brief Explanation of the Accompanying Drawings

FIG.1 is a restriction map of a recombinant DNA containing a genomic DNA according to the present invention.

Explanation of the symbols are as follows: The symbol "*Hin* dIII" indicates a cleavage site by a restriction enzyme *Hin* dIII, and the symbol "HuIGIF" indicates a genomic DNA according to the present invention.

Detailed Description of the Invention

The followings are the preferred embodiments according to the present invention. This invention is made based on the identification of a genomic DNA encoding the polypeptide with the amino acid sequence of SEQ ID NO:1 or its homologous one, and the finding that the genomic DNA efficiently expresses the polypeptide with high biological activities when introduced into mammalian host cells. The genomic DNA of the present invention usually contains two or more exons, at least one of which possesses a part of or the whole of the nucleotide sequence of

SEQ ID NO:2. The wording "a part" includes a nucleotide and a sequential nucleotides consisting of two or more nucleotides in SEQ ID NO:2. Examples of the exons are SEQ ID NOs:3 and 4. Human genomic DNA may contain additional exons with SEQ ID NOs:5 to 7. Since the present genomic DNA is derived from a mammalian genomic DNA, it contains introns, as a distinctive feature in mammalian genomic DNAs. The present genomic DNA usually has two or more introns such as SEQ ID NOs:8 to 12.

More particular examples of the present genomic DNA include DNAs with SEQ ID NOs:13 and 14 or complementary sequences thereunto. The DNAs with SEQ ID NOs:13 and 14 are substantially the same. The DNA with SEQ ID NO:14 contains coding regions for a leader peptide, consisting of the nucleotides 15,607th-15,685th, 17,057th-17,068th and 20,452nd-20,468th, coding regions for the present polypeptide, consisting of the nucleotides 20,469th-20,586th, 21,921st-22,054th and 26,828th-27,046th, and regions as introns, consisting of the nucleotides 15,686th-17,056th, 17,069-20,451st, 20,587th-21,920th and 22,055th-26,827th. The genomic DNA with SEQ ID NO:13 is suitable for expressing the polypeptide in mammalian host cells.

Generally in this field, when artificially expressing a DNA encoding a polypeptide in a host, one or more nucleotides in a DNA may be replaced by different ones, and appropriate promoter(s) and/or enhancer(s) may be linked to the DNA to improve the expressing efficiency or the properties of the expressed polypeptide. The present genomic DNA can be altered similarly as above. Therefore, as far as not substantially changing in the biological activities of the expressed

polypeptides, the present genomic DNA should include DNAs encoding functional equivalents of the polypeptide, formed as follows: One or more nucleotides in SEQ ID NOs:3 to 14 are replaced by different ones, the untranslated regions and/or the coding region for a leader peptide in the 5'- and/or 3'-termini of SEQ ID NOs:3, 4, 5, 6, 7, 13 and 14 are deleted, and appropriate oligonucleotides are linked to either or both ends of SEQ ID NO:13.

The present genomic DNA includes general DNAs which are derived from a genome containing the nucleotide sequences as above, and it is not restricted to its sources or origins as far as it is once isolated from its original organisms. For example, the present genomic DNA can be obtained by chemically synthesizing based on SEQ ID NOs:2 to 14, or by isolating from a human genomic DNA. The isolation of the present genomic DNA from such a human genomic DNA comprises (a) isolating a genomic DNA from human cells by conventional methods, (b) screening the genomic DNA with probes or primers, which are chemically synthesized oligonucleotides with a part of or the whole of the nucleotide sequence of SEQ ID NO:2, and (c) collecting a DNA to which the probes or primers specifically hybridize. Once the present genomic DNA is obtained, it can be unlimitedly replicated by constructing a recombinant DNA with an autonomously replicable vector by conventional method and then introducing the recombinant DNA into an appropriate host such as a microorganism or an animal cell before culturing the transformant or by applying a PCR method.

The present genomic DNA is very useful in producing the polypeptide by recombinant DNA techniques since it

efficiently expresses the polypeptide with high biological activities when introduced into mammalian host cells. The present invention further provides a process for preparing a polypeptide using a specific genomic DNA, comprising the steps of (a) culturing a transformant formed by introducing the present genomic DNA into mammalian host cells, and (b) collecting the polypeptide which induces IFN-γ production by immunocompetent cells from the resultant culture.

The following explains the process for preparing the polypeptide according to the present invention. The present genomic DNA is usually introduced into host cells in the form of a recombinant DNA. The recombinant DNA, comprising the present genomic DNA and an autonomously replicable vector, can be relatively easily prepared by conventional recombinant DNA techniques when the genomic DNA is available. The vectors, into which the present genomic DNA can be inserted, include plasmid vectors such as pcD, pcDL-SRα, pKY4, pCDM8, pCEV4 and pME18S. The autonomously replicable vectors usually further contain appropriate nucleotide sequences for the expression of the present recombinant DNA in each host cell, which include sequences for promoters, enhancers, replication origins, transcription termination sites, splicing sequences and/or selective markers. Heat shock protein promoters or IFN-α promoters, as disclosed in Japanese Patent Kokai No.163,368/95 by the same applicant of this invention, enables to artificially regulate the present genomic DNA expression by external stimuli.

To insert the present genomic DNA into vectors, conventional methods used in this field can be arbitrarily used: Genes containing the present genomic DNA and autonomously

replicable vectors are cleaved with restriction enzymes and/or ultrasonic, and the resultant DNA fragments and the resultant vector fragments are ligated. To cleave genes and vectors by restriction enzymes, which specifically act on nucleotides, more particularly, *Acc*I, *Bam*HI, *Bgl*II, *Bst*XI, *Eco*RI, *Hind*III, *Not*I, *Pst*I, *Sac*I, *Sal*I, *Sma*I, *Spe*I, *Xba*I, *Xho*I, etc., facilitate the ligation of the DNA fragments and the vector fragments. To ligate the DNA fragments and the vector fragments, they are, if necessary, first annealed, then treated with a DNA ligase *in vivo* or *in vitro*. The recombinant DNAs thus obtained can be unlimitedly replicated in hosts derived from microorganisms or animals.

Any cells conventionally used as hosts in this field can be used as the host cells: Examples of such are epithelial, interstitial and hemopoietic cells, derived from human, monkey, mouse and hamster, more particularly, 3T3 cells, C127 cells, CHO cells, CV-1 cells, COS cells, HeLa cells, MOP cells and their mutants. Cells which inherently produce the present polypeptide also can be used as the host cells: Example of such are human hemopoietic cells such as lymphoblasts, lymphocytes, monoblasts, monocytes, myeloblasts, myelocytes, granulocytes and macrophages, and human epithelial and interstitial cells derived from solid tumors such as pulmonary carcinoma, large bowel cancer and colon cancer. More particular examples of the latter hemopoietic cells are leukemia cell lines such as HBL-38 cells, HL-60 cells ATCC CCL240, K-562 cells ATCC CCL243, KG-1 cells ATCC CCL246, Mo cells ATCC CRL8066, THP-1 cells ATCC TIB202, U-937 cells ATCC CRL1593.2, described by J. Minowada et al. in

"*Cancer Research*", Vol.10, pp.1-18 (1988), derived from leukemias or lymphoma including myelogenous leukemias, promyelocytic leukemias, monocytic leukemias, adult T-cell leukemias and hairy cell leukemias, and their mutants. The present polypeptide-processibility of these leukemia cell lines and their mutants is so distinguished that they can easily yield the polypeptide with higher biological activities when used as hosts.

To introduce the present DNA into the hosts, conventional methods such as DEAE-dextran method, calcium phosphate transfection method, electroporation method, lipofection method, microinjection method, and viral infection method as using retrovirus, adenovirus, herpesvirus and vaccinia virus, can be used. The polypeptide-producing clones in the transformants can be selected by applying the colony hybridization method or by observing the polypeptide production after culturing the transformants in culture media. For example, the recombinant DNA techniques using mammalian cells as hosts are detailed in "*Jikken-Igaku-Bessatsu Saibo-Kogaku Handbook* (The handbook for the cell engineering)" (1992), edited by Toshio KUROKI, Masaru TANIGUCHI and Mitsuo OSHIMURA, published by YODOSHA. CO., LTD., Tokyo, Japan, and "*Jikken-Igaku-Bessatsu Biomanual Series 3 Idenshi Cloning Jikken-Ho* (The experimental methods for the gene cloning)" (1993), edited by Takahi YOKOTA and Ken-ichi ARAI, published by YODOSHA CO., LTD., Tokyo, Japan.

The transformants thus obtained secrete the present polypeptide intracellularly and/or extracellularly when cultured

in culture media. As the culture media, conventional ones used for mammalian cells can be used. The culture media generally comprise (a) buffers as a base, (b) inorganic ions such as sodium ion, potassium ion, calcium ion, phosphoric ion and chloric ion, (c) micronutrients, carbon sources, nitrogen sources, amino acids and vitamins, which are added depending on the metabolic ability of the cells, and (d) sera, hormones, cell growth factors and cell adhesion factors, which are added if necessary. Examples of individual media include 199 medium, DMEM medium, Ham's F12 medium, IMDM medium, MCDB 104 medium, MCDB 153 medium, MEM medium, RD medium, RITC 80-7 medium, RPMI-1630 medium, RPMI-1640 medium and WAJC 404 medium. The cultures containing the present polypeptide are obtainable by inoculating the transformants into the culture media to give a cell density of 1×10^4 - 1×10^7 cells/ml, more preferably, 1×10^5 - 1×10^6 cells/ml, and then subjecting to suspension- or monolayer-cultures at about 37°C for 1-7 days, more preferably, 2-4 days, while appropriately replacing the culture media with a fresh preparation of the culture media. The cultures thus obtained usually contain the present polypeptide in a concentration of about 1-100 µg/ml, which may vary depending on the types of the transformants or the culture conditions used.

While the cultures thus obtained can be used intact as an IFN-γ inducer, they are usually subjected to a step for separating the present polypeptide from the cells or the cell debris using filtration, centrifugation, etc. before use, which may follow a step for disrupting the cells with supersonication, cell-lytic enzymes and/or detergents if desired, and to a step for purifying the polypeptide. The cultures from which the

cells or cell debris are removed are usually subjected to conventional methods used in this field for purifying biologically active polypeptides, such as salting-out, dialysis, filtration, concentration, separatory sedimentation, ion-exchange chromatography, gel filtration chromatography, adsorption chromatography, chromatofocusing, hydrophobic chromatography, reversed phase chromatography, affinity chromatography, gel electrophoresis and/or isoelectric focusing. The resultant purified polypeptide can be concentrated and/or lyophilized into liquids or solids depending on final uses. The monoclonal antibodies disclosed in Japanese Patent Kokai No.231,598/96 by the same applicant of this invention are extremely useful to purify the present polypeptide. Immunoaffinity chromatography using monoclonal antibodies yields the present polypeptide in a relatively high purity at the lowest costs and labors.

The polypeptide obtainable by the process according to the present invention exerts strong effects in the treatment and/or the prevention for IFN-γ- and/or killer cell-susceptive diseases since it possesses the properties of enhancing killer cells' cytotoxicity and inducing killer cells' formation as well as inducing IFN-γ, a useful biologically active protein, as described above. The polypeptide according to the present invention has a high activity of inducing IFN-γ, and this enables a desired amount of IFN-γ production with only a small amount. The polypeptide is so low toxic that it scarcely causes serious side effects even when administered in a relatively-high dose. Therefore, the polypeptide has an advantage that it can readily induce IFN-γ in a desired amount without strictly

controlling the dosage. The uses as agents for susceptive diseases are detailed in Japanese Patent Application No.28,722/96 by the same applicant of this invention.

The present genomic DNA is also useful for so-called "gene therapy". According to conventional gene therapy, the present DNA can be introduced into patients with IFN-γ- and/or killer cell-susceptive diseases by directly injecting after the DNA is inserted into vectors derived from viruses such as retrovirus, adenovirus and adeno-associated virus or is incorporated into cationic- or membrane fusible-liposomes, or by self-transplanting lymphocytes which are collected from patients before the DNA is introduced. In adoptive immunotherapy with gene therapy, the present DNA is introduced into effector cells similarly as in conventional gene therapy. This can enhance the cytotoxicity of the effector cells to tumor cells, resulting in improvement of the adoptive immunotherapy. In tumor vaccine therapy with gene therapy, tumor cells from patients, into which the present genomic DNA is introduced similarly as in conventional gene therapy, are self-transplanted after proliferated *ex vivo* up to give a desired cell number. The transplanted tumor cells act as vaccines in the patients to exert a strong antitumor immunity specifically to antigens. Thus, the present genomic DNA exhibits considerable effects in gene therapy for diseases including viral diseases, microbial diseases, malignant tumors and immunopathies. The general procedures for gene therapy are detailed in "*Jikken-Igaku-Bessatsu Biomanual UP Series Idenshichiryo-no-Kisogijutsu* (Basic techniques for the gene therapy)" (1996), edited by Takashi

ODAJIMA, Izumi SAITO and Keiya OZAWA, published by YODOSHA CO., LTD., Tokyo, Japan.

The following examples explain the present invention, and the techniques used therein are conventional ones used in this field: For example, the techniques are described in "*Jikken-Igaku-Bessatsu Saibo-Kogaku Handbook* (The handbook for the cell engineering)", (1992), edited by Toshio KUROKI, Masaru TANIGUCHI and Mitsuo OSHIMURA, published by YODOSHA CO., LTD., Tokyo, Japan, and "*Jikken-Igaku-Bessatsu Biomanual Series 3 Idenshi Clonong Jikken-Ho* (The experimental methods for the gene cloning)" (1993), edited by Takahi YOKOTA and Ken-ichi ARAI, published by YODOSHA CO., LTD., Tokyo, Japan.

Example 1

Cloning genomic DNA and determination of nucleotide sequence

Example 1-1

Determination of partial nucleotide sequence

Five ng of "PromoterFinder™ DNA PvuII LIBRARY", a human placental genomic DNA library commercialized by CLONTECH Laboratories, Inc., California, USA, 5 μl of 10 x Tth PCR reaction solution, 2.2 μl of 25 mM magnesium acetate, 4 μl of 2.5 mM dNTP-mixed solution, one μl of the mixed solution of 2 unit/μl rTth DNA polymerase XL and 2.2 μg/μl Tth Start Antibody in a ratio of 4:1 by volume, 10 pmol of an oligonucleotide with the nucleotide sequence of 5'-CCATCCTAATACGACTCACTATAGGGC-3' as an adaptor primer, and 10 pmol of an oligonucleotide with the nucleotide sequence of 5'-TTCCTCTTCCCGAAGCTGTGTAGACTGC-3' as an anti-sense primer, which was chemically synthesized based on the sequence of the nucleotides 88th-115th in SEQ ID NO:2, were

mixed and volumed up to 50 µl with sterilized distilled water. After incubating at 94°C for one min, the mixture was subjected to 7 cycles of incubations at 94°C for 25 sec and at 72°C for 4 min, followed by 32 cycles of incubations at 94°C for 25 sec at 67°C for 4 min to perform PCR.

The reaction mixture was diluted by 100 folds with sterilized distilled water. One µl of the dilution, 5 µl of 10 x Tth PCR reaction solution, 2.2 µl of 25 mM magnesium acetate, 4 µl of 2.5 mM dNTP-mixed solution, one µl of the mixed solution of 2 unit/µl rTth DNA polymerase XL and 2.2 µg/µl Tth Start Antibody in a ratio of 4:1 by volume, 10 pmol of an oligonucleotide with the nucleotide sequence of 5'-CTATAGGGCACGCGTGGT-3' as a nested primer, and 10 pmol of an oligonucleotide with the nucleotide sequence of 5'-TTCCTCTTCCCGAAGCTGTGTAGACTGC-3' as an anti-sense primer, which was chemically synthesized similarly as above, were mixed and volumed up to 50 µl with sterilized distilled water. After incubating at 94°C for one min, the mixture was subjected to 5 cycles of incubations at 94°C for 25 sec and at 72°C for 4 min, followed by 22 cycles of incubations at 94°C for 25 sec and at 67°C for 4 min to perform PCR for amplifying a DNA fragment of the present genomic DNA. The genomic DNA library and reagents for PCR used above were mainly from "PromoterFinder™ DNA WALKING KITS", commercialized by CLONTECH Laboratories, Inc., California, USA

An adequate amount of the PCR product thus obtained was mixed with 50 ng of "pT7 Blue(R)", a plasmid vector commercialized by Novagen, Inc., WI, USA, and an adequate amount of T4 DNA ligase, and 100 mM ATP was added to give a final

concentration of one mM, followed by incubating at 16°C for 18 hr to insert the DNA fragment into the plasmid vector. The obtained recombinant DNA was introduced into an *Escherichia coli* JM109 strain by the competent cell method to form a transformant, which was then inoculated into L-broth medium (pH 7.2) containing 50 μg/ml ampicillin and cultured at 37°C for 18 hr. The cells were isolated from the resulting culture, and then subjected to the conventional alkali-SDS method to collect a recombinant DNA. The dideoxy method analysis confirmed that the recombinant DNA contained the DNA fragment with a sequence of the nucleotides 5,150th-6,709th in SEQ ID NO:14.

Example 1-2

Determination of partial nucleotide sequence

PCR was performed in the same conditions as the first PCR in Example 1-1, but an oligonucleotide with the nucleotide sequence of 5'-GTAAGTTTTCACCTTCCAACTGTAGAGTCC-3', which was chemically synthesized based on the nucleotide sequence of the DNA fragment in Example 1-1, was used as an anti-sense primer.

The reaction mixture was diluted by 100 folds with sterilized distilled water. One μl of the dilution was placed into a reaction tube, and PCR was performed in the same conditions as used in the second PCR in Example 1-1 to amplify another DNA fragment of the present genomic DNA, but an oligonucleotide with the nucleotide sequence of 5'-GGGATCAAGTAGTGATCAGAAGCAGCACAC-3', which was chemically synthesized based on the nucleotide sequence of the DNA fragment in Example 1-1, was used as an anti-sense primer.

The DNA fragment was inserted into the plasmid vector similarly as in Example 1-1 to obtain a recombinant DNA. The

recombinant DNA was replicated in *Escherichia coli* before being collected. The analysis of the collected recombinant DNA confirmed that it contained the DNA fragment with a sequence of the nucleotides 1st-5,228th in SEQ ID NO:14.

Example 1-3

Determination of partial nucleotide sequence

0.5 µg of a human placental genomic DNA, commercialized by CLONTECH Laboratories, Inc., California, USA, 5 µl of 10 x PCR reaction solution, 8 µl of 2.5 mM dNTP-mixed solution, one µl of the mixed solution of 5 unit/µl "TAKARA LA Taq POLYMERASE" and 1.1 µg/µl "TaqStart ANTIBODY" in a ratio of 1:1 by volume, both of them are commercialized by Takara Syuzo Co., Tokyo, Japan, 10 pmol of an oligonucleotide with the nucleotide sequence of 5'-CCTGGCTGCCAACTCTGGCTGCTAAAGCGG-3' as a sense primer, chemically synthesized based on a sequence of the nucleotides 46th-75th in SEQ ID NO:2, and 10 pmol of an oligonucleotide with the nucleotide sequence of 5'-GTATTGTCAATAAATTTCATTGCCACAAAGTTG-3' as an anti-sense primer, chemically synthesized based on a sequence of the nucleotides 210th-242nd in SEQ ID NO:2, were mixed and volumed up to 50 µl with sterilized distilled water. After incubating at 94°C for one min, the mixture was subjected to 5 cycles of incubations at 98°C for 20 sec and at 68°C for 10 min, followed by 25 cycles of incubations at 98°C for 20 sec and 68°C for 10 min, with adding 5 sec in times to every cycle, and finally incubated at 72°C for 10 min to amplify further DNA fragment of the present genomic DNA. The reagents for PCR used above were mainly from "TAKARA LA PCR KIT VERSION 2", commercialized by Takara Syuzo Co., Tokyo, Japan.

The DNA fragment was inserted into the plasmid vector similarly as in Example 1-1 to obtain a recombinant DNA. The recombinant DNA was replicated in *Escherichia coli* before being collected. The analysis of the collected recombinant DNA confirmed that it contained the DNA fragment with a sequence of the nucleotides 6,640th-15,671st in SEQ ID NO:14.

Experiment 1-4

Determination of partial nucleotide sequence

PCR was performed in the same conditions as the PCR in Example 1-3 to amplify further another DNA fragment of the present genomic DNA; but an oligonucleotide with the nucleotide sequence of 5'-AAGATGGCTGCTGAACCAGTAGAAGACAATTGC-3', chemically synthesized based on a sequence of the nucleotide 175th-207th in SEQ ID NO:2, was used as a sense primer, an oligonucleotide with the nucleotide sequence of 5'-TCCTTGGTCAATGAAGAGAACTTGGTC-3', chemically synthesized based on a sequence of nucleotides 334th-360th in the SEQ ID NO:2, was used as an anti-sense primer, and after incubating at 98°C for 20 sec, the reaction mixture was subjected to 30 cycles of incubations at 98°C for 20 sec and at 68°C for 3 min, followed by incubating at 72°C for 10 min.

The DNA fragment was inserted into the plasmid vector similarly as in Example 1-1 to obtain a recombinant DNA. The recombinant DNA was replicated in *Escherichia coli* before being collected. The analysis of the collected recombinant DNA confirmed that it contained the DNA fragment with a sequence of the nucleotides 15,604th-20,543rd in SEQ ID NO:14.

Example 1-5

Determination of partial nucleotide sequence

PCR was performed in the same conditions as the PCR in Example 1-4 to amplify further another DNA fragment of the present genomic DNA, but an oligonucleotide with the nucleotide sequence of 5'-CCTGGAATCAGATTACTTTGGCAAGCTTGAATC-3', chemically synthesized based on the sequence of the nucleotide 273rd-305th in SEQ ID NO:2, was used as a sense primer, and an oligonucleotide with the nucleotide sequence of 5'-GGAAATAATTTTGTTCTCACAGGAGAGAGTTG-3', chemically synthesized based on the sequence of nucleotides 500th-531st in the SEQ ID NO:2, was used as an anti-sense primer.

The DNA fragment was inserted into the plasmid vector similarly as in Example 1-1 to obtain a recombinant DNA. The recombinant DNA was replicated in *Escherichia coli* before being collected. The analysis of the collected recombinant DNA confirmed that it contained the DNA fragment with a sequence of the nucleotides 20,456th-22,048th in SEQ ID NO:14.

Example 1-6

Determination of partial nucleotide sequence

PCR was performed in the same conditions as the PCR in Example 1-4 to amplify further another DNA fragment of the present genomic DNA, but an oligonucleotide with the nucleotide sequence of 5'-GCCAGCCTAGAGGTATGGCTGTAACTATCTC-3', chemically synthesized based on the sequence of the nucleotide 449th-479th in SEQ ID NO:2, was used as a sense primer, and an oligonucleotide with the nucleotide sequence of 5'-GGCATGAAATTTTAATAGCTAGTCTTCGTTTTG-3', chemically synthesized based on the sequence of nucleotides 745th-777th in the SEQ ID NO:2, was used as an anti-sense primer.

The DNA fragment was inserted into the plasmid vector

similarly as in Example 1-1 to obtain a recombinant DNA. The recombinant DNA was replicated in *Escherichia coli* before being collected. The analysis of the collected recombinant DNA confirmed that it contained the DNA fragment with a sequence of the nucleotides 21,996th-27,067th in SEQ ID NO:14.

Example 1-7

Determination of partial nucleotide sequence

PCR was performed in the same conditions as the first PCR in Example 1-2 to amplify further another DNA fragment in the present genomic DNA, but an oligonucleotide with the nucleotide sequence of 5'-GTGACATCATATTCTTTCAGAGAAGTGTCC-3', chemically synthesized based on the sequence of the nucleotide 575th-604th in SEQ ID NO:2, was used as a sense primer.

The reaction mixture was diluted by 100 folds with sterilized distilled water. One µl of the dilution was placed into a reaction tube, and PCR was performed in the same conditions as the second PCR in Example 1-2 to amplify further another DNA fragment of the present genomic DNA, but an oligonucleotide with the sequence of 5'-GCAATTTGAATCTTCATCATACGAAGGATAC-3', chemically synthesized based on a sequence of the nucleotides 624th-654th in SEQ ID NO:2, was used as a sense primer.

The DNA fragment was inserted into the plasmid vector similarly as in Example 1-1 to obtain a recombinant DNA. The recombinant DNA was replicated in *Escherichia coli* before being collected. The analysis of the collected recombinant DNA confirmed that it contained the DNA fragment with a sequence of the nucleotides 26,914th-28,994th in SEQ ID NO:14.

Example 1-8

Determination of complete nucleotide sequence

Comparing the nucleotide sequence of SEQ ID NO:2, which was proved to encode the present polypeptide, as disclosed in Japanese Patent Kokai No.193,098/96 by the same applicant of this invention, with the partial nucleotide sequences identified in Examples 1-1 to 1-7, it was proved that the present genomic DNA contained the nucleotide sequence of SEQ ID NO:14. SEQ ID NO:14, consisting of 28,994 base pairs (bp), was extremely longer than the SEQ ID NO:2, consisting of only 471 bp. This suggested that SEQ ID NO:14 contained introns, a characteristic of eukalyotic cells.

It was examined where partial nucleotide sequences of SEQ ID NO:2, i.e., exons, and the donor and acceptor sites in introns, respectively consisting of the nucleotides of GT and AG, located in SEQ ID NO:14. Consequently, it was proved that SEQ ID NO:14 contained at least 5 introns, which located in the order of SEQ ID NOs:10, 11, 12, 8 and 9 in the direction from the 5'- to the 3'-termini. Therefore, the sequences between the neighboring introns must be exons, which were thought to be located in the order of SEQ ID NOs:5, 6, 3, 4 and 7 in the direction from the 5'- to the 3'-termini. It was also proved that SEQ ID NO:7 contained the 3'-untranslated region other than the exons. The features of the sequence elucidated as this are arranged in SEQ ID NO:14.

As disclosed in Japanese Patent Kokai No.193,098/96 by the same applicant of this invention, the present polypeptide is produced as a polypeptide with N-terminal amino acid of tyrosine other than methionine in human cells, which is observed in SEQ ID NO:1. This suggests that the present genomic DNA

contains a leader peptide region in the upstream of the 5'-terminus of the present polypeptide-encoding region. A sequence consisting of 36 amino acids encoded by the upstream of the nucleotides 20,469th-20,471st. which is the nucleotides of TAC, are described as a leader peptide in SEQ ID NO:14.

Example 2

Preparation of recombinant DNA pBGHuGF for expression

0.06 ng of the DNA fragment in Example 1-4 in a concentration of 3 ng/50 µl, 0.02 ng of the DNA fragment, obtained by the methods in Example 1-5, 5 µl of 10 x LA PCR reaction solution, 8 µl of 2.5 mM dNTP-mixed solution, one µl of the mixed solution of 5 unit/µl TAKARA LA Taq polymerase and 1.1 µg/µl TaqStart Antibody in a ratio of 1:1 by volume, 10 pmol of an oligonucleotide with the sequence of 5'-TCCGAAGCTTAAGATGGCTGCTGAACCAGTA-3' as a sense primer, chemically synthesized based on the nucleotide sequence of the DNA fragment in Example 1-4, and 10 pmol of an oligonucleotide with the nucleotide sequence of 5'-GGAAATAATTTTGTTCTCACAGGAGAGAGTTG-3' as an anti-sense primer, chemically synthesized based on the nucleotide sequence of the DNA fragment in Example 1-5, were mixed and volumed up to 50 µl with sterilized distilled water. After incubating at 94°C for one min, the mixture was subjected to 5 cycles of incubations at 98°C for 20 sec and at 72°C for 7 min, followed by 25 cycles of incubations at 98°C for 20 sec and 68°C for 7 min to perform PCR. The reaction mixture was cleaved by restriction enzymes *Hin*dIII and *Sph*I to obtain a DNA fragment of about 5,900 bp, with cleavage sites by *Hin*dIII and *Sph*I in its both termini.

PCR was performed in the same condition as above, but 0.02 ng of the DNA fragment in Example 1-5, 0.06 ng of the DNA fragment obtained in Example 1-6, an oligonucleotide with the nucleotide sequence of 5'-ATGTAGCGGCCGCGGCATGAAATTTTAATAGCTAGTC-3' as an anti-sense primer, chemically synthesized based on the nucleotide sequence of the DNA fragment in Example 1-6, and an oligonucleotide with the sequence of 5'-CCTGGAATCAGATTACTTTGGCAAGCTTGAATC-3' as a sense primer, chemically synthesized based on the DNA fragment in Example 1-6, were used. The reaction mixture was cleaved by restriction enzymes *Not*I and *Sph*I to obtain a DNA fragment of about 5,600 bp, with cleavage sites by *Not*I and *Sph*I in its both termini.

A plasmid vector "pRc/CMV", containing a *cytomegalovirus* promoter, commercialized by Invitrogen Corporation, San Diego, USA, was cleaved by restriction enzymes *Hind*III and *Not*I to obtain a vector fragment of about 5,500 bp. The vector fragment was mixed with the above two DNA fragments of about 5,900 bp and 5,600 bp, and reacted with T4 DNA ligase to insert the two DNA fragments into the plasmid vector. An *Escherichia coli* JM109 strain was transformed with the obtained recombinant DNA, and the transformant with the plasmid vector was selected by the colony hybridization method. The selected recombinant DNA was named as "pBGHuGF". As shown in FIG.1, the present genomic DNA, with the nucleotide sequence of SEQ ID NO:13, was ligated in the downstream of the cleavage site by the restriction enzyme *Hind*III in the recombinant DNA.

Example 3

Preparation of transformant using CHO cell as host

CHO-K1 cells ATCC CCL61 were inoculated into Ham's F12 medium (pH 7.2) containing 10 v/v % bovine fetal serum and proliferated by conventional manner. The proliferated cells were collected and washed with phosphate-buffered saline (hereinafter abbreviated as "PBS") followed by suspending in PBS to give a cell density of 1×10^7 cells/ml.

10 µg of the recombinant DNA pBGHuGF in Example 2 and 0.8 ml of the above cell suspension were placed in a cuvette and ice-chilled for 10 min. The cuvette was installed in "GENE PULSER", an electroporation device commercialized by Bio-Rad Laboratories Inc., Brussels, Belgium, and then pulsed once with an electric discharge. After pulsing, the cuvette was immediately took out and ice-chilled for 10 min. The cell suspension from the cuvette was inoculated into Ham's F12 medium (pH 7.2) containing 10 v/v % bovine fetal serum and cultured under an ambient condition of 5 v/v % CO_2 at 37°C for 3 days. To the culture medium was added G-418 to give a final concentration of 400 µg/ml, and the culturing was continued further 3 weeks under the same conditions. From abut 100 colonies formed, 48 colonies were selected, and a portion of each was inoculated into a well of culturing plates with Ham's F12 medium (pH7.2) containing 400 µg/ml G-418 and 10 v/v % bovine fetal serum and cultured similarly as above. Thereafter, to each well of the culturing plates was added 10 mM Tris-HCl buffer (pH 8.5) containing 5.1 mM magnesium chloride, 0.5 w/v % sodium deoxycholate, 1 w/v % NONIDET P-40, 10 µg/ml aprotinin and 0.1 w/v % SDS to lyse the cells.

50 µl aliquot of the cell lysates was mixed with one ml of glycerol and incubated at 37°C for one hour, before the

polypeptides in the cell lysates were separated by the SDS-polyacrylamide gel electrophoresis. The separated polypeptides were transferred to a nitrocellulose membrane in usual manner, and the membrane was soaked in the culture supernatant of the hybridoma H-1, disclosed in Japanese Patent Kokai No.231,598/96 by the same applicant of this invention, followed by washing with 50 mM Tris-HCl buffer containing 0.05 v/v % TWEEN 20 to remove an excessive mount of the monoclonal antibody. Thereafter, the nitrocellulose membrane was soaked in PBS containing rabbit-derived anti-mouse immunoglobulin antibody for one hr, which was labeled with horseradish peroxidase, followed by washing 50 mM Tris-HCl buffer (pH 7.5) containing 0.05 v/v % TWEEN 20 and soaking in 50 mM Tris-HCl buffer (pH 7.5) containing 0.005 v/v % hydrogen peroxide and 0.3 mg/ml diaminobenzidine to develop colorations. The clone, which highly produced the polypeptide, was selected based on the color development and named "BGHuGF".

Example 4

Production of polypeptide by transformant and its physicochemical properties

The transformant BGHuGF in Experiment 3 was inoculated into Ham's F12 medium (pH 7.2) containing 400 μg/ml G-418 and 10 v/v % bovine fetal serum, and cultured under an ambient condition of 5 v/v % CO_2 at 37°C for one week. The proliferated cells were collected, washed with PBS, and then washing with 10-fold volumes of ice-chilled 20 mM Hepes buffer (pH 7.4), containing 10 mM potassium chloride and 0.1 mM ethylendiaminetetraacetate bisodium salt, according to the method described in "*Proceedings of The National Academy of The*

Sciences of The USA", vol.86, pp.5,227-5,231 (1989), by M. J. Kostura et al. The cells thus obtained were allowed to stand in 3-fold volumes of a fresh preparation of the same buffer under an ice-chilling condition for 20 min and freezed at -80°C, succeeded by thawing to disrupt the cells. The resulting cells were centrifuged to collect the supernatant.

In parallel, THP-1 cells ATCC TIB 202, derived from a human acute monocytic leukemia, was similarly cultured and disrupted. Supernatant, obtained by centrifuging the resulting cells, was mixed with the supernatant obtained from the transformant BGHuGF and incubated at 37°C for 3 hr to react. The reaction mixture was applied to a column with "DEAE-SEPHAROSE", a gel for ion-exchange chromatography, commercialized by Pharmacia LKB Biotechnology AB, Upsalla, Sweden, equilibrated with 10 mM phosphate buffer (pH 6.6) before use. After washing the column with 10 mM phosphate buffer (pH 6.6), 10 mM phosphate buffer (pH 6.6) with a stepwise gradient of NaCl increasing from 0 M to 0.5 M was fed to the column, and fractions eluted by about 0.2 M NaCl were collected. The fractions were dialyzed against 10 mM phosphate buffer (pH 6.8) before applied to a column with "DEAE 5PW", a gel for ion-exchange chromatography, commercialized by TOSOH Corporation, Tokyo, Japan. To the column was fed 10 mM phosphate buffer (pH 6.8) with a linear gradient of NaCl increasing from 0 M to 0.5 M, and fractions eluted by about 0.2-0.3 M NaCl were collected.

While the obtained fractions were pooled and dialyzed against PBS, a gel for immunoaffinity chromatography with the monoclonal antibody were prepared according to the method disclosed in Japanese Patent Kokai No.231,598/96 by the same

applicant of this invention. After the gel were charged into a plastic column and washed with PBS, the above dialyzed solution was applied to the column. To the column was fed 100 mM glycine-HCl buffer (pH 2.5), and the eluted fractions, which contained a polypeptide capable of inducing the production of IFN-γ by immunocompetent cells, were collected. After the collected fractions were dialyzed against sterilized distilled water and concentrated with a membrane filtration, the resultant was lyophilized to obtain a purified solid polypeptide in a yield of about 15 mg/l-culture.

Example for Reference

Expression in Escherichia coli

As disclosed in Japanese Patent Kokai No.193,098/96, a transformant pKHuGF which was obtained by introducing a cDNA with the nucleotide sequence of SEQ ID NO:2 into Escherichia coli as a host, was inoculated into L-broth medium containing 50 μg/ml ampicillin and cultured at 37°C for 18 hr under shaking conditions. The cells were collected by centrifuging the resulting culture, and then suspended in a mixture solution (pH 7.2) of 139 mM NaCl, 7 mM NaH_2PO_4 and 3 mM Na_2HPO_4, followed by supersonicating to disrupt the cells. After the cell disruptants were centrifuged, the supernatant was subjected to purifying steps similarly as in Example 4-1 to obtain a purified solid polypeptide in a yield of about 5 mg/l-culture.

Comparing the yields of the polypeptides in Example for Reference and in Example 4-1 shows that the use of a transformant, which is formed by introducing a genomic DNA encoding the present polypeptide into a mammalian cell as a host, strongly elevates the yield of the polypeptide per

culture.

Example 4-2

Physicochemical property of polypeptide

Example 4-2(a)

Biological activity

Blood were collected from a healthy donor by using a syringe containing heparin, and then diluted with 2-fold volume of serum-free RPMI-1640 medium (pH 7.4). The blood was overlaid on ficoll, commercialized by Pharmacia LKB Biotechnology AB, Upsalla, Sweden, and centrifuged to obtain lymphocytes, which were then washed with RPMI-1640 medium containing 10 v/v % bovine fetal serum before being suspended in a fresh preparation of the same medium to give a cell density of 5×10^6 cells/ml. 0.15 ml aliquots of the cell suspension was distributed into wells of micro plates with 96 wells.

To the wells with the cells were distributed 0.05 ml aliquots of solutions of the polypeptide in Example 4-1, diluted with RPMI-1640 medium (pH 7.4) containing 10 v/v % bovine fetal serum to give desired concentrations. 0.05 ml aliquots of fresh preparations of the same medium with or without 2.5 μg/ml concanavalin A or 50 units/ml recombinant human interleukin 2 were further added to the wells, before culturing in a 5 v/v % CO_2 incubator at 37°C for 24 hr. After the cultivation, 0.1 ml of the culture supernatant was collected from each well and examined on IFN-γ by usual enzyme immunoassay. In parallel, a systems as a control using the polypeptide in Reference for that in Example 4-1 or using no polypeptide was treated similarly as above. The results were in Table 1. IFN-γ in Table 1 were expressed with international units (IU), calculated based on the

IFN-γ standard, Gg23-901-530, obtained from the International Institute of Health, USA

Table 1

Sample of polypeptide	IFN-γ production (IU/ml)
Example 4-2(a)	3.4×10^5
Example for Reference	1.7×10^5

Table 1 indicates that the lymphocytes as immunocompetent cells produce IFN-γ by the action of the present polypeptide. The IFN-γ production is enhanced in combination with concanavalin A or interleukin 2 as a cofactor.

It is more remarkable that the polypeptide in Example 4-1 could induce IFN-γ production more than that in Example for Reference. Considering this and the difference in the yields of the polypeptides, described in Example for Reference, it can be presumed: Even if DNAs could be substantially equivalent in encoding the same amino acid sequence, not only the expressing efficiencies of the DNAs may differ, but the products expressed by them may significantly differ in their biological activities as a result of post-translational modifications by intracellular enzymes, depending on types of the DNAs and their hosts; (a) one type is used a transformant formed by introducing a DNA, which is a cDNA, into a microorganisms as a host, and (b) other type is used a transformant formed by introducing the present genomic DNA into a mammalian cell as a host.

Example 4-2(b)

Molecular weight

SDS-polyacrylamide gel electrophoresis of the polypeptide in Example 4-1 in the presence of 2 w/v % dithiothreitol as a reducing agent, according to the method reported by U. K. Laemli et al., in "Nature", Vol.227, pp.680-685 (1970), exhibited a main band of a protein capable of inducing IFN-γ in a position corresponding to a molecular weight of about 18,000-19,500 daltons. The molecular weight makers used in the analysis were bovine serum albumin (67,000 daltons), ovalbumin (45,000 daltons), carbonic anhydrase (30,000 daltons), soy bean trypsin inhibitor (20,100 daltons) and α-lactoalbumin (14,000 daltons).

Example 4-2(c)

N-Terminal amino acid sequence

Conventional analysis using "MODEL 473A", a protein sequencer commercialized by Perkin-Elmer Corp., Norwalk, USA, revealed that the polypeptide in Example 4-1 had the amino acid sequence of SEQ ID NO:15 in the N-terminal region.

Judging collectively from this result as well as the information that SDS-polyacrylamide gel electrophresis exhibited a main band in a position corresponding to a molecular weight of about 18,000-19,500 daltons, and that the molecular weight calculated from the amino acid sequence of SEQ ID NO:1 was 18,199 daltons, it can be concluded that the polypeptide in Example 4-1 has the amino acid sequence of SEQ ID NO:6.

As is described above, the present invention is made based on the identification of a genomic DNA encoding the polypeptide which induces the production of IFN-γ by immunocompetent cells. The present genomic DNA efficiently express the present polypeptide when introduced into mammalian

host cells. The polypeptide features higher biological activities than that obtained by the cDNA expression in *Escherichia coli*. Therefore, the present genomic DNA is useful for the recombinant DNA techniques to prepare the polypeptide capable of inducing IFN-γ production by immunocompetent cells. The present genomic DNA is useful to gene therapy for diseases including viral diseases, bacterial-infectious diseases, malignant tumors and immunopathies.

Thus, the present invention is a significant invention which has a remarkable effect and gives a great contribution to this field.

While there has been described what is at present considered to be the preferred embodiments of the present invention, it will be understood the various modifications may be made therein, and it is intended to cover in the appended claims all such modifications as fall within the true spirits and scope of the invention.

WHAT IS CLAIMED IS:

1. A composition comprising an isolated DNA molecule comprising a nucleotide sequence encoding the amino acid sequences shown in SEQ ID NO:1, where Xaa is isoleucine or threonine, and a carrier capable of introducing the isolated DNA molecule into a mammalian cell, wherein said nucleotide sequence consists of the sequence of a fragment of human genomic DNA.

2. A method for treating IFN-γ and/or killer cell-susceptive diseases using gene therapy, comprising administering the composition according to claim 1 to a subject in need thereof.

3. A method for treating tumors using gene therapy, comprising the steps of:

transforming tumor cells obtained from a subject in need thereof with the composition according to claim 1;

proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject in need thereof.

4. The composition according to claim 1, wherein the nucleotide sequence comprises an exon having the sequence shown in SEQ ID NO:3, 4, 5, 6, or 7.

5. The composition according to claim 1, wherein the nucleotide sequence comprises an intron having the sequence shown in SEQ ID NO:8, 9, 10, 11, or 12.

6. The composition according to claim 1, wherein the nucleotide sequence is the sequence shown in SEQ ID NO:13, 14, or 15.

7. The composition according to claim 1, wherein the carrier is a virus or liposome.

8. A method for treating IFN-γ and/or killer cell-susceptive diseases using gene therapy, comprising administering the composition according to claim 7 to a subject in need thereof.

9. A method for treating tumors using gene therapy, comprising the steps of:

transforming tumor cells obtained from a subject in need thereof with the composition according to claim 7;

proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject in need thereof.

10. The composition according to claim 1, wherein the isolated DNA molecule is linked with a heterologous nucleotide sequence.

11. A method for treating IFN-γ and/or killer cell-susceptive diseases using gene therapy, comprising administering the composition according to claim 10 to a subject in need thereof.

12. A method for treating tumors using gene therapy, comprising administering the steps of:

transforming tumor cells obtained from a subject in need thereof with the composition according to claim 10;

proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject in need thereof.

13. The composition according to claim 6, wherein the heterologous nucleotide sequence is of a virus vector.

14. A method for treating IFN-γ and/or killer cell-susceptive diseases using gene therapy, comprising administering the composition according to claim 13 to a subject in need thereof.

15. A method for treating tumors using gene therapy, comprising the steps of:

transforming tumor cells obtained from a subject in need thereof with the composition according to claim 13;

proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject in need thereof.

16. A method for treating IFN-γ- and/or killer cell-susceptive diseases using gene therapy, comprising administering to a subject in need thereof an isolated DNA molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:1, where Xaa is isoleucine or threonine, wherein the nucleotide sequence consists of the sequence of a fragment of human genomic DNA.

17. A method for treating tumors using gene therapy, comprising the steps of:

transforming tumor cells obtained from a subject in need thereof with an isolated DNA molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:1, where Xaa is isoleucine or threonine, wherein the nucleotide sequence consists of the sequence of a fragment of human genomic DNA;

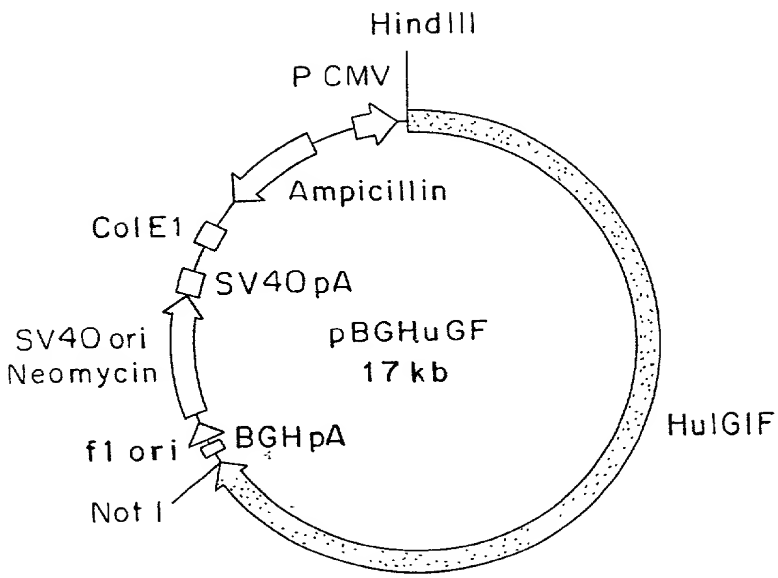
proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject in need thereof.

Abstract of the Disclosure

Disclosed is a genomic DNA encoding a polypeptide capable of inducing the production of interferon-γ by immunocompetent cells. The genomic DNA efficiently expresses the polypeptide with high biological activities of such as inducing the production of interferon-γ by immunocompetent cells, enhancing killer cells' cytotoxicity and inducing killer cells' formation, when introduced into mammalian host cells. The high biological activities of the polypeptide facilitate its uses to treat and/or prevent malignant tumors, viral diseases, bacterial infectious diseases and immune diseases without serious side effects when administered to humans.

FIG. 1


HindIII
P CMV
Ampicillin
ColE1
SV40 pA
pBGHuGF
17 kb
SV40 ori
Neomycin
f1 ori
BGH pA
Not I
HuIGIF

 [X] Original [ ] Supplemental Atty.Docket:

Combined Declaration for Patent Application and Power of Attorney

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and that I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

(insert full title here) GENOMIC DNA ENCODING A POLYPEPTIDE CAPABLE OF INDUCING THE PRODUCTION OF INTERFERON-GAMMA

the specification of which (check one)

[X] is attached hereto;

[ ] was filed in the United States under 35 U.S.C. §111 on ____________, as USSN ____________*; or

[ ] was/will be filed in the U.S. under 35 U.S.C. §371 by entry into the U.S. national stage of an international (PCT) application, PCT/____________; filed ____________, entry requested on ____________*; national stage application received USSN ____________*; §371/§102(e) date ____________* (*if known),

and was amended on ______________________________ (if applicable).

(include dates of amendments under PCT Art. 19 and 34 if PCT)

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above; and I acknowledge the duty to disclose to the Patent and Trademark Office (PTO) all information known by me to be material to patentability as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §§ 119, 365 of any prior foreign application(s) for patent or inventor's certificate, or prior PCT application(s) designating a country other than the U.S., listed below with the "Yes" box checked and have also identified below any such application having a filing date before that of the application on which priority is claimed:

(Number)	(Country)	(Day Month Year Filed)	YES	NO
185305/1996	Japan	27th June 1996	[X]	[ ]
			[ ]	[ ]
			[ ]	[ ]

I hereby claim the benefit under 35 U.S.C. § 120 of any prior U.S. non-provisional Application(s) or prior PCT Application(s) designating the U.S. listed below, or under § 119(e) of any prior U.S. provisional applications listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in such U.S. or PCT application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the PTO all information as defined in 37 C.F.R. §1.56(a) which occurred between the filing date of the prior application and the national filing date of this application:

(Application Serial No.)	(Day Month Year Filed)	(Status: patented, pending, abandoned)

I hereby appoint the following attorneys, with full power of substitution, association, and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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Atty.Docket:

Title: GENOMIC DNA ENCODING A POLYPEPTIDE CAPABLE OF INDUCING THE PRODUCTION OF INTERFERON-GAMMA

U.S. Application filed ____________, Serial No. ____________

PCT Application filed ____________, Serial No. ____________

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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FULL NAME OF SECOND JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Kakuji TORIGOE	Kakuji Torigoe	June 17, '97
RESIDENCE: Okayama, Japan	CITIZENSHIP: Japanese	
POST OFFICE ADDRESS: 1343-5, Fujito, Fujito-cho, Kurashiki-shi, Okayama, Japan		

FULL NAME OF THIRD JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Masashi KURIMOTO	Masashi Kurimoto	June 17, '97
RESIDENCE: Okayama, Japan	CITIZENSHIP: Japanese	
POST OFFICE ADDRESS: 7-25, Gakunan-cho 2-chome, Okayama-shi, Okayama, Japan		

FULL NAME OF FOURTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE:	CITIZENSHIP:	
POST OFFICE ADDRESS:		

FULL NAME OF FIFTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE:	CITIZENSHIP:	
POST OFFICE ADDRESS:		

FULL NAME OF SIXTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE:	CITIZENSHIP:	
POST OFFICE ADDRESS:		

FULL NAME OF SEVENTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE:	CITIZENSHIP:	
POST OFFICE ADDRESS:		

ALL INVENTORS MUST REVIEW APPLICATION AND DECLARATION BEFORE SIGNING. ALL ALTERATIONS MUST BE INITIALED AND DATED BY ALL INVENTORS PRIOR TO EXECUTION. NO ALTERATIONS CAN BE MADE AFTER THE DECLARATION IS SIGNED. ALL PAGES OF DECLARATION MUST BE SEEN BY ALL INVENTORS.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Takanori OKURA
Kakuji TORIGOE
Masahi KURIMOTO

(ii) TITLE OF INVENTION: GENOMIC DNA ENCODING A POLYPEPTIDE CAPABLE OF INDUCING THE PRODUCTION OF INTERFERON-γ

(iii) NUMBER OF SEQUENCES: 35

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: BROWDY AND NEIMARK
(B) STREET: 419 Seventh Street, N.W., Suite 300
(C) CITY: Washington
(D) STATE: D.C.
(E) COUNTRY: USA
(F) ZIP: 20004

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: Patent In Release #1.0, Version #1.30

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: JP 185,305/96
(B) FILING DATE: 27-JUN-1996

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: BROWDY, Roger L.
(B) REGISTRATION NUMBER: 25,618
(C) REFERENCE/DOCKET NUMBER: OKURA=1

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 202-628-5197
(B) TELEFAX: 202-737-3528

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 157 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
1               5                   10                  15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
            20                  25                  30
Met Thr Asp Ser Asp Cys Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
        35                  40                  45
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile
    50                  55                  60
Ser Val Lys Cys Glu Lys Ile Ser Xaa Leu Ser Cys Glu Asn Lys Ile
65                  70                  75                  80
Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys
                85                  90                  95
Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys
            100                 105                 110
Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu
        115                 120                 125
```

```
Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu
    130                 135                 140
Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp
145                 150                 155
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1120 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: No

(iv) ANTI-SENSE: No

(vi) ORIGINAL SOURCE:
- (A) ORGANISM: human
- (F) TISSUE TYPE: liver

(iX) FEATURE:
- (A) NAME/KEY: 5'UTR
- (B) LOCATION: 1..177
- (C) IDENTIFICATION METHODS: E
- (A) NAME/KEY: leader peptide
- (B) LOCATION: 178..285
- (C) IDENTIFICATION METHODS: S
- (A) NAME/KEY: mat peptide
- (B) LOCATION: 286..756
- (C) IDENTIFICATION METHODS: S
- (A) NAME/KEY: 3'UTR
- (B) LOCATION: 757..1120
- (C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
GCCTGGACAG TCAGCAAGGA ATTGTCTCCC AGTGCATTTT GCCCTCCTGG CTGCCAACTC    60
TGGCTGCTAA AGCGGCTGCC ACCTGCTGCA GTCTACACAG CTTCGGGAAG AGGAAAGGAA   120
CCTCAGACCT TCCAGATCGC TTCCTCTCGC AACAAACTAT TTGTCGCAGG AATAAAG      177
ATG GCT GCT GAA CCA GTA GAA GAC AAT TGC ATC AAC TTT GTG GCA ATG     225
Met Ala Ala Glu Pro Val Glu Asp Asn Cys Ile Asn Phe Val Ala Met
    -35                 -30                 -25
AAA TTT ATT GAC AAT ACG CTT TAC TTT ATA GCT GAA GAT GAT GAA AAC     273
Lys Phe Ile Asp Asn Thr Leu Tyr Phe Ile Ala Glu Asp Asp Glu Asn
-20                 -15                 -10                  -5
CTG GAA TCA GAT TAC TTT GGC AAG CTT GAA TCT AAA TTA TCA GTC ATA     321
Leu Glu Ser Asp Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile
                1               5                   10
AGA AAT TTG AAT GAC CAA GTT CTC TTC ATT GAC CAA GGA AAT CGG CCT     369
Arg Asn Leu Asn Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro
        15                  20                  25
CTA TTT GAA GAT ATG ACT GAT TCT GAC TGT AGA GAT AAT GCA CCC CGG     417
Leu Phe Glu Asp Met Thr Asp Ser Asp Cys Arg Asp Asn Ala Pro Arg
    30                  35                  40
ACC ATA TTT ATT ATA AGT ATG TAT AAA GAT AGC CAG CCT AGA GGT ATG     465
Thr Ile Phe Ile Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met
45                  50                  55                  60
GCT GTA ACT ATC TCT GTG AAG TGT GAG AAA ATT TCA AYT CTC TCC TGT     513
Ala Val Thr Ile Ser Val Lys Cys Glu Lys Ile Ser Xaa Leu Ser Cys
                65                  70                  75
GAG AAC AAA ATT ATT TCC TTT AAG GAA ATG AAT CCT CCT GAT AAC ATC     561
Glu Asn Lys Ile Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile
            80                  85                  90
AAG GAT ACA AAA AGT GAC ATC ATA TTC TTT CAG AGA AGT GTC CCA GGA     609
```

Lys Asp Thr Lys Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly
95 100 105

CAT GAT AAT AAG ATG CAA TTT GAA TCT TCA TCA TAC GAA GGA TAC TTT 657
His Asp Asn Lys Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe
110 115 120
CTA GCT TGT GAA AAA GAG AGA GAC CTT TTT AAA CTC ATT TTG AAA AAA 705
Leu Ala Cys Glu Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys
125 130 135 140
GAG GAT GAA TTG GGG GAT AGA TCT ATA ATG TTC ACT GTT CAA AAC GAA 753
Glu Asp Glu Leu Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu
145 150 155
GAC TAGCTATTAA AATTTCATGC CGGGCGCAGT GGCTCACGCC TGTAATCCCA 806
Asp
GCCCTTTGGG AGGCTGAGGC GGGCAGATCA CCAGAGGTCA GGTGTTCAAG ACCAGCCTGA 866
CCAACATGGT GAAACCTCAT CTCTACTAAA AATACTAAAA ATTAGCTGAG TGTAGTGACG 926
CATGCCCTCA ATCCCAGCTA CTCAAGAGGC TGAGGCAGGA GAATCACTTG CACTCCGGAG 986
GTAGAGGTTG TGGTGAGCCG AGATTGCACC ATTGCGCTCT AGCCTGGGCA ACAACAGCAA 1046
AACTCCATCT CAAAAAATAA AATAAATAAA TAAACAAATA AAAAATTCAT AATGTGAAAA 1106
AAAAAAAAAA AAAA 1120

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 135 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 1..135
(C) IDENTIFICATION METHODS: S

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

AA AAC CTG GAA TCA GAT TAC TTT GGC AAG CTT GAA TCT AAA TTA TCA 47
Glu Asn Leu Glu Ser Asp Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser
-5 1 5 10
GTC ATA AGA AAT TTG AAT GAC CAA GTT CTC TTC ATT GAC CAA GGA AAT 95
Val Ile Arg Asn Leu Asn Asp Gln Val Leu Phe Ile Asp Gln Gly Asn
15 20 25
CGG CCT CTA TTT GAA GAT ATG ACT GAT TCT GAC TGT AGA G 135
Arg Pro Leu Phe Glu Asp Met Thr Asp Ser Asp Cys Arg Asp
30 35 40

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 134 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 1..134
(C) IDENTIFICATION METHODS: S

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
 AT AAT GCA CCC CGG ACC ATA TTT ATT ATA AGT ATG TAT AAA GAT AGC     47
Asp Asn Ala Pro Arg Thr Ile Phe Ile Ile Ser Met Tyr Lys Asp Ser
40                  45                  50                  55
CAG CCT AGA GGT ATG GCT GTA ACT ATC TCT GTG AAG TGT GAG AAA ATT     95
Gln Pro Arg Gly Met Ala Val Thr Ile Ser Val Lys Cys Glu Lys Ile
                60                  65                  70
TCA ACT CTC TCC TGT GAG AAC AAA ATT ATT TCC TTT AAG                134
Ser Thr Leu Ser Cys Glu Asn Lys Ile Ile Ser Phe Lys
            80                  85
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 1..87
(C) IDENTIFICATION METHODS: S

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
GAATAAAG ATG GCT GCT GAA CCA GTA GAA GAC AAT TGC ATC AAC TTT GTG    50
         Met Ala Ala Glu Pro Val Glu Asp Asn Cys Ile Asn Phe Val
             -35                 -30                 -25
GCA ATG AAA TTT ATT GAC AAT ACG CTT TAC TTT ATA G                   87
Ala Met Lys Phe Ile Asp Asn Thr Leu Tyr Phe Ile Ala
        -20                 -15                 -10
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 1..87
(C) IDENTIFICATION METHODS: S

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

CT GAA GAT GAT G 12
Ala Glu Asp Asp Glu
-10

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2167 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: exon + 3'UTR
(B) LOCATION: 1..2167
(C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GAA ATG AAT CCT CCT GAT AAC ATC AAG GAT ACA AAA AGT GAC ATC ATA 48
Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys Ser Asp Ile Ile
85 90 95 100
TTC TTT CAG AGA AGT GTC CCA GGA CAT GAT AAT AAG ATG CAA TTT GAA 96
Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys Met Gln Phe Glu
105 110 115
TCT TCA TCA TAC GAA GGA TAC TTT CTA GCT TGT GAA AAA GAG AGA GAC 144
Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu Lys Glu Arg Asp
120 125 130
CTT TTT AAA CTC ATT TTG AAA AAA GAG GAT GAA TTG GGG GAT AGA TCT 192
Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu Gly Asp Arg Ser
135 140 145
ATA ATG TTC ACT GTT CAA AAC GAA GAC TAGCTAT TAAAATTTCA TGCCGGGCGC 246
Ile Met Phe Thr Val Gln Asn Glu Asp
150 155
AGTGGCTCAC GCCTGTAATC CCAGCCCTTT GGGAGGCTGA GGCGGGCAGA TCACCAGAGG 306
TCAGGTGTTC AAGACCAGCC TGACCAACAT GGTGAAACCT CATCTCTACT AAAAATACAA 366
AAAATTAGCT GAGTGTAGTG ACCCATGCCC TCAATCCCAG CTACTCAAGA GGCTGAGGCA 426
GGAGAATCAC TTGCACTCCG GAGGTGGAGG TTGTGGTGAG CCGAGATTGC ACCATTGCGC 486
TCTAGCCTGG GCAACAACAG CAAAACTCCA TCTCAAAAAA TAAAATAAAT AAATAAACAA 546
ATAAAAAATT CATAATGTGA ACTGTCTGAA TTTTTATGTT TAGAAAGATT ATGAGATTAT 606
TAGTCTATAA TTGTAATGGT GAAATAAAAT AAATACCAGT CTTGAAAAAC ATCATTAAGA 666
AATGAATGAA CTTTCACAAA AGCAAACAAA CAGACTTTCC CTTATTTAAG TGAATAAAAT 726
AAAATAAAAT AAAATAATGT TTAAAAAATT CATAGTTTGA AAACATTCTA CATTGTTAAT 786
TGGCATATTA ATTATACTTA ATATAATTAT TTTTAAATCT TTTGGGTTAT TAGTCCTAAT 846
GACAAAAGAT ATTGATATTT GAACTTTCTA ATTTTTAAGA ATATCGTTAA ACCATCAATA 906
TTTTTATAAG GAGGCCACTT CACTTGACAA ATTTCTGAAT TTCCTCCAAA GTCAGTATAT 966
TTTTAAAATT CAGTTTGATC CTGAATCCAG CAATATATAA AAGGGATTAT ATACTCTGGC 1026
CAACTGACAT TCATCCTAGG AATGCAAAGA TGGTTTAATA TCCTAAAATC AATTAACATA 1086
ACATACTATA TTAATAAAGT ATCAAAACAG TATTCTCATC TTTTTTTCTT TTTTCACAAT 1146
TCCTTGGTTA CACTATCATC TCAATAGATG CAGAAAAAGC ATTTGACAAA ATCCAATTCA 1206
TAATAAAAAT TCTCAAACTT GAAAGAGAAC ATCATAAAGG CATCTATGAA AAACCTACAG 1266
CTAATATCAT ACTTAACGAT GAAAAACTGA ATTATTTTAC CCTAAGATCA AGAATAATGC 1326
AAGCATGTCA GCTCTTGCAA CTTCTATTCA ACATTGTACT GGAGGTTCTA GCCAGAGCAA 1386
CCATACAATA AATAAAAATA AAAGGCACCC AGATTAGAAA GGAAGTCTTT ATTTGCAGAC 1446
AACATGGTTC TTTATGCAGA AAACCGTCAG GAATACACAC ACATGTTAGA ACTAATAAGT 1506
TCAGCAAGGT TGCAGGTTGC AATATCAATA TGCAAAAATA CATTGAAGGC TGGGCTCAGT 1566
GGAGATGGCA TGTACCTTTC GTCCCAGCTA CTTGGGAGGC TGAGGTAGGA GGATCACTTG 1626
AGGTGAGGAG TTTGAGGCTA TAGTGCAATG TGATCTTGCC TGTGAATAGC CACTGCACTC 1686
GAGCCTAGGC AACAAAGTGA GACCCCGTCT CCAAAAAAAA AAATGGTATA TTGGTATTTC 1746
TGTATATGAA CAATGAATGA TCTGAAAACA AGAAAATTCC ATTCACGATG GTATTAAAAA 1806
AATAAAATAC AAATAAATTT AGCAAAATAA TTATAAAACT TGTACATCGA AAATTTCAAA 1866

GCACTCTGAG GGAAATTAAA GATGATCTAA ATAATTGGAG AGACACTCTA TGATCACTGA 1926
TTGGAAAATT CATTCAATAT TGTTAAGATA ACAATTGTCC CCAAATTGAT GCATGCATTC 1986
AATTTAGTCT TCATCAAAAT TCCAGCAGGG TTTTTGCAGA AATTGACAAG CTGTACCCAA 2046
AATGTATATG GAAATGAAAA GACCCAGAAG AGCAAATAAT TTTTTAAAAA CAAAGTTGGA 2106
AAACTTTTAC TTCCTAATTT TAAAACTTAC TATAAACCTA AAGTTATCAA GACCATTTAG 2166
T 2167

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1334 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: intron
(B) LOCATION: 1..1334
(C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GTATTTTTTT TAATTCGCAA ACATAGAAAT GACTAGCTAC TTCTTCCCAT TCTGTTTTAC 60
TGCTTACATT GTTCCGTGCT AGTCCCAATC CTCAGATGAA AAGTCACAGG AGTGACAATA 120
ATTTCACTTA CAGGAAACTT TATAAGGCAT CCACGTTTTT TAGTTGGGGT AAAAAATTGG 180
ATACAATAAG ACATTGCTAG GGGTCATGCC TCTCTGAGCC TGCCTTTGAA TCACCAATCC 240
CTTTATTGTG ATTGCATTAA CTGTTTAAAA CCTCTATAGT TGGATGCTTA ATCCCTGCTT 300
GTTACAGCTG AAAATGCTGA TAGTTTACCA GGTGTGGTGG CATCTATCTG TAATCCTAGC 360
TACTTGGGAG GCTCAAGCAG GAGGATTGCT TGAGGCCAGG ACTTTGAGGC TGTAGTACAC 420
TGTGATCGTA CCTGTGAATA GCCACTGCAC TCCAGCCTGG GTGATATACA GACCTTGTCT 480
CTAAAATTAA AAAAAAAAAA AAAAAAAACC TTAGGAAAGG AAATTGATCA AGTCTACTGT 540
GCCTTCCAAA ACATGAATTC CAAATATCAA AGTTAGGCTG AGTTGAAGCA GTGAATGTGC 600
ATTCTTTAAA AATACTGAAT ACTTACCTTA ACATATATTT TAAATATTTT ATTTAGCATT 660
TAAAAGTTAA AAACAATCTT TTAGAATTCA TATCTTTAAA ATACTCAAAA AAGTTGCAGC 720
GTGTGTGTTG TAATACACAT TAAACTGTGG GGTTGTTTGT TTGTTTGAGA TGCAGTTTCA 780
CTCTGTCACC CAGGCTGAAG TGCAGTGCAG TGCAGTGGTG TGATCTCGGC TCACTACAAC 840
CTCCACCTCC CACGTTCAAG CGATTCTCAT GCCTCAGTCT CCCGAGTAGG TGGGATTACA 900
GGCATGCACC ACTTACACCC GGCTAATTTT TGTATTTTTA GTAGAGCTGG GGTTTCACCA 960
TGTTGGCCAG GCTGGTCTCA AACCCCTAAC CTCAAGTGAT CTGCCTGCCT CAGCCTCCCA 1020
AACAAACAAA CAACCCCACA GTTTAATATG TGTTACAACA CACATGCTGC AACTTTTATG 1080
AGTATTTTAA TGATATAGAT TATAAAAGGT TGTTTTTAAC TTTTAAATGC TGGGATTACA 1140
GGCATGAGCC ACTGTGCCAG GCCTGAACTG TGTTTTTAAA AATGTCTGAC CAGCTGTACA 1200
TAGTCTCCTG CAGACTGGCC AAGTCTCAAA GTGGGAACAG GTGTATTAAG GACTATCCTT 1260
TGGTTAAATT TCCGCAAATG TTCCTGTGCA AGAATTCTTC TAACTAGAGT TCTCATTTAT 1320
TATATTTATT TCAG 1334

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4773 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:

(A) NAME/KEY: intron
(B) LOCATION: 1..4773
(C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

```
GTAAGACTGA GCCTTACTTT GTTTTCAATC ATGTTAATAT AATCAATATA ATTAGAAATA   60
TAACATTATT TCTAATGTTA ATATAAGTAA TGTAATTAGA AAACTCAAAT ATCCTCAGAC  120
CAACCTTTTG TCTAGAACAG AAATAACAAG AAGCAGAGAA CCATTAAAGT GAATACTTAC  180
TAAAAATTAT CAAACTCTTT ACCTATTGTG ATAATGATGG TTTTTCTGAG CCTGTCACAG  240
GGGAAGAGGA GATACAACAC TTGTTTTATG ACCTGCATCT CCTGAACAAT CAGTCTTTAT  300
ACAAATAATA ATGTAGAATA CATATGTGAG TTATACATTT AAGAATAACA TGTGACTTTC  360
CAGAATGAGT TCTGCTATGA AGAATGAAGC TAATTATCCT TCTATATTTC TACACCTTTG  420
TAAATTATGA TAATATTTTA ATCCCTAGTT GTTTTGTTGC TGATCCTTAG CCTAAGTCTT  480
AGACACAAGC TTCAGCTTCC AGTTGATGTA TGTTATTTTT AATGTTAATC TAATTGAATA  540
AAAGTTATGA GATCAGCTGT AAAAGTAATG CTATAATTAT CTTCAAGCCA GGTATAAAGT  600
ATTTCTGGCC TCTACTTTTT CTCTATTATT CTCCATTATT ATTCTCTATT ATTTTTCTCT  660
ATTTCCTCCA TTATTGTTAG ATAAACCACA ATTAACTATA GCTACAGACT GAGCCAGTAA  720
GAGTAGCCAG GGATGCTTAC AAATTGGCAA TGCTTCAGAG GAGAATTCCA TGTCATGAAG  780
ACTCTTTTTG AGTGGAGATT TGCCAATAAA TATCCGCTTT CATGCCCACC CAGTCCCCAC  840
TGAAAGACAG TTAGGATATG ACCTTAGTGA AGGTACCAAG GGGCAACTTG GTAGGGAGAA  900
AAAAGCCACT CTAAAATATA ATCCAAGTAA GAACAGTGCA TATGCAACAG ATACAGCCCC  960
CAGACAAATC CCTCAGCTAT CTCCCTCCAA CCAGAGTGCC ACCCCTTCAG GTGACAATTT 1020
GGAGTCCCCA TTCTAGACCT GACAGGCAGC TTAGTTATCA AAATAGCATA AGAGGCCTGG 1080
GATGGAAGGG TAGGGTGGAA AGGGTTAAGC ATGCTGTTAC TGAACAACAT AATTAGAAGG 1140
GAAGGAGATG GCCAAGCTCA AGCTATGTGG GATAGAGGAA AACTCAGCTG CAGAGGCAGA 1200
TTCAGAAACT GGGATAAGTC CGAACCTACA GGTGGATTCT TGTTGAGGGA GACTGGTGAA 1260
AATGTTAAGA AGATGGAAAT AATGCTTGGC ACTTAGTAGG AACTGGGCAA ATCCATATTT 1320
GGGGGAGCCT GAAGTTTATT CAATTTTGAT GGCCCTTTTA AATAAAAAGA ATGTGGCTGG 1380
GCGTGGTGGC TCACACCTGT AATCCCAGCA CTTTGGGAGG CCGAGGGGGG CGGATCACCT 1440
GAAGTCAGGA GTTCAAGACC AGCCTGACCA ACATGGAGAA ACCCCATCTC TACTAAAAAT 1500
ACAAAATTAG CTGGGCGTGG TGGCATATGC CTGTAATCCC AGCTACTCGG GAGGCTGAGG 1560
CAGGAGAATC TTTTGAACCC GGGAGGCAGA GGTTGCGATG AGCCTAGATC GTGCCATTGC 1620
ACTCCAGCCT GGGCAACAAG AGCAAAACTC GGTCTCAAAA AAAAAAAAAA AAAAGTGAAA 1680
TTAACCAAAG GCATTAGCTT AATAATTTAA TACTGTTTTT AAGTAGGGCG GGGGGTGGCT 1740
GGAAGAGATC TGTGTAAATG AGGGAATCTG ACATTTAAGC TTCATCAGCA TCATAGCAAA 1800
TCTGCTTCTG GAAGGAACTC AATAAATATT AGTTGGAGGG GGGGAGAGAG TGAGGGGTGG 1860
ACTAGGACCA GTTTTAGCCC TTGTCTTTAA TCCCTTTTCC TGCCACTAAT AAGGATCTTA 1920
GCAGTGGTTA TAAAAGTGGC CTAGGTTCTA GATAATAAGA TACAACAGGC CAGGCACAGT 1980
GGCTCATGCC TATAATCCCA GCACTTTGGG AGGGCAAGGC GAGTGTCTCA CTTGAGATCA 2040
GGAGTTCAAG ACCAGCCTGG CCAGCATGGC GATACTCTGT CTCTACTAAA AAAAATACAA 2100
AAATTAGCCA GGCATGGTGG CATGCACCTG TAATCCCAGC TACTCGTGAG CCTGAGGCAG 2160
AAGAATCGCT TGAAACCAGG AGGTGTAGGC TGCAGTGAGC TGAGATCGCA CCACTGCACT 2220
CCAGCCTGGG CGACAGAATG AGACTTTGTC TCAAAAAAAG AAAAAGATAC AACAGGCTAC 2280
CCTTATGTGC TCACCTTTCA CTGTTGATTA CTAGCTATAA AGTCCTATAA AGTTCTTTGG 2340
TCAAGAACCT TGACAACACT AAGAGGGATT TGCTTTGAGA GGTTACTGTC AGAGTCTGTT 2400
TCATATATAT ACATATACAT GTATATATGT ATCTATATCC AGGCTTGGCC AGGGTTCCCT 2460
CAGACTTTCC AGTGCACTTG GGAGATGTTA GGTCAATATC AACTTTCCCT GGATTCAGAT 2520
TCAACCCCTT CTGATGTAAA AAAAAAAAAA AAAAAGAAAG AAATCCCTTT CCCCTTGGAG 2580
CACTCAAGTT TCACCAGGTG GGGCTTTCCA AGTTGGGGGT TCTCCAAGGT CATTGGGATT 2640
GCTTTCACAT CCATTTGCTA TGTACCTTCC CTATGATGGC TGGGAGTGGT CAACATCAAA 2700
ACTAGGAAAG CTACTGCCCA AGGATGTCCT TACCTCTATT CTGAAATGTG CAATAAGTGT 2760
GATTAAAGAG ATTGCCTGTT CTACCTATCC ACACTCTCGC TTTCAACTGT AACTTTCTTT 2820
TTTTCTTTTT TTCTTTTTTT CTTTTTTTTT GAAACGGAGT CTCGCTCTGT CGCCCAGGCT 2880
AGAGTGCAGT GGCACGATCT CAGCTCACTG CAAGCTCTGC CTCCCGGGTT CACGCCATTC 2940
TCCTGCCTCA CCCTCCCAAG CAGCTGGGAC TACAGGCGCC TGCCACCATG CCCAGCTAAT 3000
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TGAACTTGTG ATCCGCCCGC CTCAGCCTCC CAAAGTGCTG GGATTACAGG CGTGAGCCAT 3120
CGCACCCGGC TCAACTGTAA CTTTCTATAC TGGTTCATCT TCCCCTGTAA TGTTACTAGA 3180
GCTTTTGAAG TTTTGGCTAT GGATTATTTC TCATTTATAC ATTAGATTTC AGATTAGTTC 3240
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GGTGGTGCCC ACATGTTCTG ATCCATCCTG CAAAATAGAC ATGCTGCACT AACAGGAAAA 3660
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(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8835 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: intron
(B) LOCATION: 1..8835
(C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

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ATAGAAGCCA TATAGATCTG CTGGATTCTC ATCTGCTTTG CATTCAGACT ACTGCAATAT 420
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(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1371 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: intron
(B) LOCATION: 1..1371
(C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

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CCTTGTCACA CCACGTGTCC TGGCACTTTA ATCAGCAGTA GCTCACTCTC CAGTTGGCAG   240
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(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3383 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: intron
(B) LOCATION: 1..3383
(C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

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(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11464 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: 5'UTR
(B) LOCATION: 1..3
(C) IDENTIFICATION METHODS: E
(A) NAME/KEY: leader peptide
(B) LOCATION: 4..82
(C) IDENTIFICATION METHODS: S

(A) NAME/KEY: intron
(B) LOCATION: 83..1453
(C) IDENTIFICATION METHODS: E
(A) NAME/KEY: leader peptide
(B) LOCATION: 1454..1465
(C) IDENTIFICATION METHODS: S
(A) NAME/KEY: intron
(B) LOCATION: 1466..4848
(C) IDENTIFICATION METHODS: E
(A) NAME/KEY: leader peptide
(B) LOCATION: 4849..4865
(C) IDENTIFICATION METHODS: S
(A) NAME/KEY: mat peptide
(B) LOCATION: 4866..4983
(C) IDENTIFICATION METHODS: S
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(B) LOCATION: 4984..6317
(C) IDENTIFICATION METHODS: E
(A) NAME/KEY: mat peptide
(B) LOCATION: 6318..6451
(C) IDENTIFICATION METHODS: S
(A) NAME/KEY: intron
(B) LOCATION: 6452..11224
(C) IDENTIFICATION METHODS: E
(A) NAME/KEY: mat peptide
(B) LOCATION: 11225..11443
(C) IDENTIFICATION METHODS: S
(A) NAME/KEY: 3'UTR
(B) LOCATION: 11444..11464
(C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

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Met Lys Phe Ile Asp Asn Thr Leu Tyr Phe Ile Ala
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Cys Arg Asp
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Glu Met Asn
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Arg Ser Val Pro Gly His Asp Asn Lys Met Gln Phe Glu Ser Ser Ser
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Leu Ile Leu Lys Lys Glu Asp Glu Leu Gly Asp Arg Ser Ile Met Phe
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ACT GTT CAA AAC GAA GAC TAGCTATTAA AATTTCATGC C 11464
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155

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28994 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(F) TISSUE TYPE: placenta

(iX) FEATURE:
(A) NAME/KEY: 5'UTR
(B) LOCATION: 1..15606
(C) IDENTIFICATION METHODS: E
(A) NAME/KEY: leader peptide
(B) LOCATION: 15607..15685
(C) IDENTIFICATION METHODS: S
(A) NAME/KEY: intron
(B) LOCATION: 15686..17056
(C) IDENTIFICATION METHODS: E
(A) NAME/KEY: leader peptide
(B) LOCATION: 17057..17068
(C) IDENTIFICATION METHODS: S
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(B) LOCATION: 17069..20451
(C) IDENTIFICATION METHODS: E
(A) NAME/KEY: leader peptide
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(C) IDENTIFICATION METHODS: S
(A) NAME/KEY: mat peptide
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(C) IDENTIFICATION METHODS: S
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(B) LOCATION: 20587..21920
(C) IDENTIFICATION METHODS: E
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(C) IDENTIFICATION METHODS: S
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(C) IDENTIFICATION METHODS: E
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(B) LOCATION: 26828..27046
(C) IDENTIFICATION METHODS: S
(A) NAME/KEY: 3'UTR
(B) LOCATION: 27047..28994
(C) IDENTIFICATION METHODS: E

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

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                                                 Glu Met Asn Pro
                                                 85
CCT GAT AAC ATC AAG GAT ACA AAA AGT GAC ATC ATA TTC TTT CAG AGA     26887
Pro Asp Asn Ile Lys Asp Thr Lys Ser Asp Ile Ile Phe Phe Gln Arg
    90                  95                  100
AGT GTC CCA GGA CAT GAT AAT AAG ATG CAA TTT GAA TCT TCA TCA TAC     26935
Ser Val Pro Gly His Asp Asn Lys Met Gln Phe Glu Ser Ser Ser Tyr
105                 110                 115                 120
GAA GGA TAC TTT CTA GCT TGT GAA AAA GAG AGA GAC CTT TTT AAA CTC     26983
Glu Gly Tyr Phe Leu Ala Cys Glu Lys Glu Arg Asp Leu Phe Lys Leu
                125                 130                 135
ATT TTG AAA AAA GAG GAT GAA TTG GGG GAT AGA TCT ATA ATG TTC ACT     27031
Ile Leu Lys Lys Glu Asp Glu Leu Gly Asp Arg Ser Ile Met Phe Thr
            140                 145                 150
GTT CAA AAC GAA GAC T AGCTATTAAA ATTTCATGCC GGGCGCAGTG GCTCACGCCT  27087
Val Gln Asn Glu Asp
        155
GTAATCCCAG CCCTTTGGGA GGCTGAGGCG GGCAGATCAC CAGAGGTCAG GTGTTCAAGA  27147
CCAGCCTGAC CAACATGGTG AAACCTCATC TCTACTAAAA ATACAAAAAA TTAGCTGAGT  27207
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GTAGTGACCC ATGCCCTCAA TCCCAGCTAC TCAAGAGGCT GAGGCAGGAG AATCACTTGC  27267
ACTCCGGAGG TGGAGGTTGT GGTGAGCCGA GATTGCACCA TTGCGCTCTA GCCTGGGCAA  27327
CAACAGCAAA ACTCCATCTC AAAAAATAAA ATAAATAAAT AAACAAATAA AAAATTCATA  27387
ATGTGAACTG TCTGAATTTT TATGTTTAGA AAGATTATGA GATTATTAGT CTATAATTGT  27447
AATGGTGAAA TAAAATAAAT ACCAGTCTTG AAAAACATCA TTAAGAAATG AATGAACTTT  27507
CACAAAAGCA AACAAACAGA CTTTCCCTTA TTTAAGTGAA TAAAATAAAA TAAAATAAAA  27567
TAATGTTTAA AAAATTCATA GTTTGAAAAC ATTCTACATT GTTAATTGGC ATATTAATTA  27627
TACTTAATAT AATTATTTTT AAATCTTTTG GGTTATTAGT CCTAATGACA AAAGATATTG  27687
ATATTTGAAC TTTCTAATTT TTAAGAATAT CGTTAAACCA TCAATATTTT TATAAGGAGG  27747
CCACTTCACT TGACAAATTT CTGAATTTCC TCCAAAGTCA GTATATTTTT AAAATTCAGT  27807
TTGATCCTGA ATCCAGCAAT ATATAAAAGG GATTATATAC TCTGGCCAAC TGACATTCAT  27867
CCTAGGAATG CAAAGATGGT TTAATATCCT AAAATCAATT AACATAACAT ACTATATTAA  27927
TAAAGTATCA AAACAGTATT CTCATCTTTT TTTCTTTTTT CACAATTCCT TGGTTACACT  27987
ATCATCTCAA TAGATGCAGA AAAAGCATTT GACAAAATCC AATTCATAAT AAAAATTCTC  28047
AAACTTGAAA GAGAACATCA TAAAGGCATC TATGAAAAAC CTACAGCTAA TATCATACTT  28107
AACGATGAAA AACTGAATTA TTTTACCCTA AGATCAAGAA TAATGCAAGC ATGTCAGCTC  28167
TTGCAACTTC TATTCAACAT TGTACTGGAG GTTCTAGCCA GAGCAACCAT ACAATAAATA  28227
AAAATAAAAG GCACCCAGAT TAGAAAGGAA GTCTTTATTT GCAGACAACA TGGTTCTTTA  28287
TGCAGAAAAC CGTCAGGAAT ACACACACAT GTTAGAACTA ATAAGTTCAG CAAGGTTGCA  28347
GGTTGCAATA TCAATATGCA AAAATACATT GAAGGCTGGG CTCAGTGGAG ATGGCATGTA  28407
CCTTTCGTCC CAGCTACTTG GGAGGCTGAG GTAGGAGGAT CACTTGAGGT GAGGAGTTTG  28467
AGGCTATAGT GCAATGTGAT CTTGCCTGTG AATAGCCACT GCACTCGAGC CTAGGCAACA  28527
AAGTGAGACC CCGTCTCCAA AAAAAAAAAT GGTATATTGG TATTTCTGTA TATGAACAAT  28587
GAATGATCTG AAAACAAGAA AATTCCATTC ACGATGGTAT TAAAAAAATA AAATACAAAT  28647
AAATTTAGCA AAATAATTAT AAAACTTGTA CATCGAAAAT TTCAAAGCAC TCTGAGGGAA  28707
ATTAAAGATG ATCTAAATAA TTGGAGAGAC ACTCTATGAT CACTGATTGG AAAATTCATT  28767
CAATATTGTT AAGATAACAA TTGTCCCCAA ATTGATGCAT GCATTCAATT TAGTCTTCAT  28827
CAAAATTCCA GCAGGGTTTT TGCAGAAATT GACAAGCTGT ACCCAAAATG TATATGGAAA  28887
TGAAAAGACC CAGAAGAGCA AATAATTTTT TAAAAACAAA GTTGGAAAAC TTTTACTTCC  28947
TAATTTTAAA ACTTACTATA AACCTAAAGT TATCAAGACC ATTTAGT                28994
```

(15) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal fragment

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

```
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
CCATCCTAAT ACGACTCACT ATAGGGC                                          27
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TTCCTCTTCC CGAAGCTGTG TAGACTGC 28

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTATAGGGCA CGCGTGGT 18

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TTCCTCTTCC CGAAGCTGTG TAGACTGC 28

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GTAAGTTTTC ACCTTCCAAC TGTAGAGTCC 30

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GGGATCAAGT CGTGATCAGA AGCAGCACAC 30

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CCTGGCTGCC AACTCTGGCT GCTAAAGCGG 30

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTATTGTCAA TAAATTTCAT TGCCACAAAG TTG 33

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

AAGATGGCTG CTGAACCAGT AGAAGACAAT TGC 33

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

TCCTTGGTCA ATGAAGAGAA CTTGGTC 27

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CCTGGAATCA GATTACTTTG GCAAGCTTGA ATC 33

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GGAAATAATT TTGTTCTCAC AGGAGAGAGT TG 32

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GCCAGCCTAG AGGTATGGCT GTAACTATCT C 31

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGCATGAAAT TTTAATAGCT AGTCTTCGTT TTG 33

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GTGACATCAT ATTCTTTCAG AGAAGTGTCC 30

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GCAATTTGAA TCTTCATCAT ACGAAGGATA C 31

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TCCGAAGCTT AAGATGGCTG CTGAACCAGT A 31

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GGAAATAATT TTGTTCTCAC AGGAGAGAGT TG 32

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATGTAGCGGC CGCGGCATGA AATTTTAATA GCTAGTC 37

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CCTGGAATCA GATTACTTTG GCAAGCTTGA ATC 33